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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of

VIAL et al.

Atty. Ref.: 1721-83

Serial No. 10/521,329

Group: 1614

Filed: January 14, 2005

Examiner: Unknown

For: COMPOUNDS WITH ANTI-PARASITIC ACTIVITY AND MEDICAMENTS CONTAINING THEM

* * * * * * * * * * * *

November 30, 2005

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

SUBMISSION

Submitted herewith is a copy of the International Preliminary Examination Report in the English language for the above-referenced application.

Respectfully submitted,

NIXON & VANDERHYE P.C.

By: _____
B. J. Sadoff
Reg. No. 36,663

BJS:pp
901 North Glebe Road, 11th Floor
Arlington, VA 22203-1808
Telephone: (703) 816-4000
Facsimile: (703) 816-4100

Translation

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference CP 60735PCT	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/FR2003/002283	International filing date (*day/month/year*) 18 juillet 2003 (18.07.2003)	Priority date (*day/month/year*) 18 juillet 2002 (18.07.2002)
International Patent Classification (IPC) or national classification and IPC A61K 31/155, 31/4245, 31/506, A61P 33/06, 33/00		
Applicant CENTRE NATIONAL DE LA RECHERCHE SCIENTIFIQUE (CNRS)		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 14 sheets, including this cover sheet.

☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

These annexes consist of a total of _____ sheets.

3. This report contains indications relating to the following items:

- I ☒ Basis of the report
- II ☐ Priority
- III ☒ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV ☒ Lack of unity of invention
- V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- VI ☐ Certain documents cited
- VII ☐ Certain defects in the international application
- VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
18 février 2004 (18.02.2004)	06 December 2004 (06.12.2004)
Name and mailing address of the IPEA/EP Facsimile No.	Authorized officer Telephone No.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002283

I. Basis of the report

1. With regard to the **elements** of the international application:*

☒ the international application as originally filed

☒ the description:

pages 1-67, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the claims:

pages 1-29, as originally filed
pages _____, as amended (together with any statement under Article 19
pages _____, filed with the demand
pages _____, filed with the letter of _____

☒ the drawings:

pages 1/1, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

☐ the sequence listing part of the description:

pages _____, as originally filed
pages _____, filed with the demand
pages _____, filed with the letter of _____

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).

☐ the language of publication of the international application (under Rule 48.3(b)).

☐ the language of the translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

☐ the description, pages _____

☐ the claims, Nos. _____

☐ the drawings, sheets/fig _____

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rule 70.16 and 70.17).*

** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002283

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application.

☒ claims Nos. 5,7-24,28,29

because:

☐ the said international application, or the said claims Nos. _____ relate to the following subject matter which does not require an international preliminary examination *(specify)*:

☒ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. 5,22,28,29 are so unclear that no meaningful opinion could be formed *(specify)*:

See supplemental sheet

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 7-21, 23,24 .

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002283

IV. Lack of unity of invention

1. In response to the invitation to restrict or pay additional fees the applicant has:

☐ restricted the claims.

☐ paid additional fees.

☐ paid additional fees under protest.

☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

☐ complied with.

☐ not complied with for the following reasons:

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☐ all parts.

☐ the parts relating to claims Nos. _____

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/FR2003/002283

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims		YES
	Claims		NO
Inventive step (IS)	Claims		YES
	Claims		NO
Industrial applicability (IA)	Claims		YES
	Claims		NO

2. Citations and explanations

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

The application does not fulfil the requirements set forth in PCT Article 6 because claims 5, 22, 24, 28 and 29 are not clear.

1. Groups a1, a2 and a4, which are mentioned in claim 24, are not defined in any of claims 1-29. Claim 24 is dependent on claim 23 ("a method for producing amidoxime derivatives of general formula (X)". Even though groups a1, a2 and a4 are defined on pages 4 and 5 of the description, claim 24 lacks clarity under the terms of PCT Article 6.

   It is, in fact, chemically impossible to produce compounds of general formula (VI) (group a2), general formula (VIII) (group a4) or general formula (V) (group a1) using the method of claim 23.

   The compounds of general formulae (V) and (VI) are bis-amidines and those of general formula (VIII) are bis-oxadiazoles, while the compounds of general formula (X) (claim 23) are N,N'disubstituted diamines.

   Since no search was carried out with respect to claim 24, no opinion shall be established as to the patentability of the subject matter of claim 24.

2. The expression "while R3 and/or R'3, R2 and/or R'2 represent a hydrogen atom, R1, R2 and R3" in claim 5 is not clear under the terms of PCT Article 6.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: III.1

3. The expression "anti-parasitic diseases" in claims 28 and 29 lacks clarity under the terms of PCT Article 6. On the basis of the description (anti-parasitic compounds and parasitic diseases), said expression has been interpreted as meaning "parasitic diseases".

4. The use of substituents R3 and R'3 either to describe the substitution in formula (V) (R3 = R'3 = H) or to define compounds R3Cl and R'3Cl (R3, R'3 ≠ H) renders claim 22 imprecise. It has been assumed that R in the RCl "derivatives" can mean all of the groups defined for R3 or R'3 (except for hydrogen).

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

1. The present Authority considers that the claims cover the following 5 inventions:

1.1 Claims: 1-6, 22 and 25-29 (all in part)

Compounds having general formula (I) wherein X is a group of formula (II) in which n = 0, i.e. the compounds as per formula (V), with the exception of the heterocyclic compounds as per formulae (VI) and (VII); a method for producing the carbamates and the N-phosphorylated derivatives thereof; pharmaceutical compositions containing the compounds of formula (V), with the exception of the compounds as per formulae (VI) and (VII); and the use thereof in the preparation of drugs for treating parasitic diseases, in particular, malaria and babesiosis.

1.2 Claims: 15-20 and 23 and, in part, 1, 2, 14 and 25-29

Compounds having general formula (I) wherein Y is a group of formula (III) in which n = 0, i.e. the compounds as per formula (IX) wherein n = 0 (the compounds of formula (X)); a method for producing the amidoxime derivatives thereof; pharmaceutical compositions containing the compounds of formula (X) and the use thereof in the preparation of drugs for treating parasitic diseases, in particular, malaria and babesiosis.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

1.3 Claims: 1, 2, 14 and 25-29 (all in part)

Compounds having general formula (I) wherein Y is a group of formula (III) in which n = 1, or wherein X is a group of formula (II) in which n = 1, i.e. the compounds as per formulae (IV) in which n = 1, or (IX) in which n = 1; pharmaceutical compositions containing said compounds and the use of same in the preparation of drugs for treating parasitic diseases, in particular, malaria and babesiosis.

1.4 Claims: 7-13 and, in part, 1, 2, 22 and 25-29.

Heterocyclic compounds having formula (VI) or (VII); a method for producing the carbamates and the N-phosphorylated derivatives thereof; pharmaceutical compositions containing the compounds of formula (VI) or (VII) and the use thereof in the preparation of drugs for treating parasitic diseases, in particular, malaria and babesiosis.

1.5 Claims: 21 and, in part, 1, 2, 14 and 25-29

Compounds having formula (XI); pharmaceutical compositions containing said compounds and the use thereof in the preparation of drugs for treating parasitic diseases, in particular, malaria and babesiosis.

The present application relates to 5 inventions

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

that are not so linked as to form a single general inventive concept, as required by PCT Rule 13.1, for the following reasons:

2. Technical problem

The technical problem that the present invention is intended to solve is that of providing novel chemical compounds and pharmaceutical compositions containing said compounds, preparation methods therefor and the use thereof in the preparation of a drug for treating parasitic diseases.

3. Solution

The solution proposed by the present invention involves the use of the compounds having general formula (I).

4. Prior art (see also Box V, point 1, hereinafter)

Document FR 1 542 163 discloses bis-amidino compounds that have bactericidal, fungicidal, anti-protozoal, anthelmintic, antinematodal, herbicidal and insecticidal activity" (page 1, left-hand column, paragraph 1; page 21, right-hand column, paragraph 3).

Document XP008026750 discloses Synthalin (decamethylene diguanidine) as a trypanocidal agent.

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

Document XP001184129 discloses that 1,11-undecane diamidine has activity against *Plasmodium knowlesi* in monkeys and that a curative effect has been demonstrated in the treatment of malaria, even though the compound is significantly toxic and the effect thereof risky (page 278, lines 2-6).

Document XP001184130 discloses that 1,11-undecane diamidine can be used to cure permanently diseases associated with trypanosomes and that it has activity against infections with *Plasmodium vivax* (malaria) (page 103, paragraph 1; page 107, paragraph 4).

5. General inventive concept and "special technical features" (PCT Rule 13)

The compounds of general formula (I) are known in the prior art. The fact that said compounds can be used as anti-parasitic agents is also known.

Since these two technical features are not novel, they cannot, under the terms of PCT Rule 13.2, constitute "special technical features" that could unite the various inventions identified in paragraph 1 above.

The concept of using the following compounds in the treatment of parasitic diseases is known from the prior art:

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

(A) compounds having general formula (I) wherein X is a group of formula (II) in which n = 0, with the exception of the heterocyclic compounds as per formulae (VI) and (VII); or

(B) compounds having general formula (I) wherein X is a group of formula (II) in which n = 1, or

(C) compounds having general formula (I) wherein Y is a group of formula (III) in which n = 1

As a result, said concept cannot constitute a special technical feature that could amount to an inventive concept that could link said groups (A)-(C) either to one another or to

(D) the heterocyclic "bis-amidines" having formula (VI) or (VII) as well as

(E) the compounds having formula (XI).

In the present application, it has not been possible to identify any other technical feature that could constitute a "special technical feature" common to the various inventions.

The patent application relates to a plurality of inventions or groups of inventions under the terms of PCT Rule 13. These inventions have been grouped

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

Continuation of: IV.3

together in the manner defined in point 1 above.

Each of the inventions mentioned constitutes a separate invention characterised by its own special technical feature that determines a contribution made by each of the claimed inventions over the prior art (namely, the structural nature of the various groups of compounds).

6. Claim 24 has not been taken into consideration when analysing the lack of unity because claim 24 lacks clarity under the terms of PCT Article 6 (see Box III, point 1).

7. A search report was established with respect only to invention 1 as defined in point 1.1 above.

As a result, the application will be examined on the basis of the invention that has already been searched, namely the first invention mentioned in the claims (see point 1.1).

V. **Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Claims	22	YES
	Claims	1-6, 25-29	NO
Inventive step (IS)	Claims		YES
	Claims	1-6, 22, 25-29	NO
Industrial applicability (IA)	Claims	1-6, 22, 25-29	YES
	Claims		NO

2. Citations and explanations

1. Reference is made to the following documents:

D1: FR-A-1 542 163;

D2: The Lancet (11-12-1937), 233, 1360-1363 (XP008026750);

D3: Annals of Tropical Medicine and Parasitology, Academic Press, London, GB (1938), 32, 257-278 (XP001184129);

D4: Annals of Tropical Medicine and Parasitology, Academic Press, London, GB (1938), 32, 103-107 (XP001184130);

D5: Pharmazie in Unserer Zeit 1989 Germany (1989), 18(4), 97-111 (XP008026858);

D6: Tropical Diseases Bulletin (1940), 37(6), 405-406 (XP008026479);

D9: Journal of the American Chemical Society (1953), 75, 950-952 (XP002268257);

D7: Journal of Medicinal Chemistry, American Chemical Society, Washington, US (1996), 39, 3139-3147 (XP002185840);

D8: Journal of Medicinal Chemistry (23-09-1999), 42(19), 3994-4000 (XP002270580).

2. Novelty (PCT Article 33(2))

The present application does not fulfil the requirements set forth in PCT Article 33(1) because, in light of the disclosures in documents D1 and D3-D6, the subject matter of claims 1-6 and 25-29 does not comply with the requirement of novelty defined in PCT Article 33(2).

2.1 The subject matter of claims 1-6 relates to compounds of formula (I) but does not restrict the use thereof to a use as anti-parasitic agents.

2.2 Prior art

Document FR 1 542 163 A (D1) discloses bis-amidine compounds that have bactericidal, fungicidal, anti-protozoal, anthelmintic, antinematodal, herbicidal and insecticidal activity" (page 1, left-hand column, paragraph 1; page 21, right-hand column, paragraph 3).

The disclosure in document D1 deprives the subject matter of claims 1-6 and 25-29 of novelty.

Document XP001184129 (D3) discloses the anti-malarial activity of n-undecane diamidine in monkeys

(*Macacus rhesus*).

Document XP001184130 (D4) discloses the anti-malarial and trypanocidal activity of n-undecane diamidine.

Document XP008026858 (D5) discloses that aliphatic diamidines of general formula $H_2N-C(=NH)-(CH_2)_n-C(=NH)-NH_2$ (n=10-14) have trypanocidal activity (page 105, column 2, paragraph 5 to column 3, paragraph 1).

Document XP008026479 (D6) discloses that certain aliphatic diamidines, in particular, n-undecane diamidine, are effective in controlling *Babesia canis* infections.

The disclosures in each of documents D3-D6 are prejudicial to the novelty of claims 1-4 and 25-29 of the first invention.

It follows that the subject matter of claims 1-6 and 25-29 is not considered to comply with the requirement of novelty defined in PCT Article 33(2).

Even if the aforementioned claims were rendered novel by means, for example, of appropriate amendments thereto, the following objections with regard to inventive step would still remain.

3. **Inventive step (PCT Article 33(3))**

The present application does not fulfil the requirements set forth in PCT Article 33(1) because the subject matter of claims 1-6, 22 and 25-29 does

not involve an inventive step as defined in PCT Article 33(3).

3.1 Claims 5 and 6 (R1, R'1, R2, R'2, R3 and/or R'3 ≠ hydrogen)

3.1.1 Technical problem

The technical problem that the present invention aims to solve in claims 5 and 6 is that of providing novel chemical compounds, pharmaceutical compositions containing said compounds and the use of same in the preparation of a drug for treating parasitic diseases.

3.1.2 Solution

The proposed solution is to use N-substituted amidines as per formula (V) wherein one or more substituents R1, R'1, R2, R'2, R3 and/or R'3 are different to a hydrogen atom.

3.1.3 Prior art

Documents D1 and D3-D6: see point 2.2 above.

Documents XP002185840 (D7) and XP002270580 (D8): disclose the use of amidino carbamates as prodrugs for the amidines (D11: page 3141, left-hand column, paragraph 3; D8: the abstract).

3.1.4 A person skilled in the art, aware of the disclosure in D7 or D8 and the antiparasitic activity of bis-amidines as per general formula (V) in which R_1,

R'_1, R_2, R'_2, R_3 and R'_3 = H, would try using the carbamates or other derivatives of said amidines in the preparation of a drug for treating parasitic diseases and would do so without exercising any inventive skill.

Document D1, which discloses that non-substituted as well as substituted bis-amidino compounds have antiparasitic activity, would further encourage a person skilled in the art to try using these derivatives as antiparasitic agents.

3.1.5 It follows that no inventive step can be recognised with regard to the subject matter of claims 5 and 6.

3.2 The synthesis of the compounds (claim 22)

3.2.1 Technical problem

The technical problem addressed in claim 22 is that of providing a novel method for producing carbamates and N-phosphorylated derivatives having general formula (V).

3.2.2 Solution

The proposed solution is a method including a step of reacting, in a diphasic medium, bis-amidine compounds of general formula (V) wherein R_3=R'_3=H with an R_3-Cl or R'_3-Cl derivative in which R_3 and R'_3 are as defined above and different from H (see also the objection in Box III, point 4).

3.2.3 Prior art

Document XP002185840 (D7) discloses the preparation of an arylamidine carbamate with a chloroformate in a diphasic system containing dichloromethane and an aqueous sodium hydroxide solution.

Document XP002268257 (D9) discloses the preparation of di-p-nitrobenzyloxycarbonyl arginine using p-nitrobenzoic chloroformate in a diphasic system containing dioxane and an aqueous sodium hydroxide solution.

3.2.4 A person skilled in the art, aware of the disclosures in D7 and D9, would try synthesising carbamates of general formula (V) using a chloroformate in a biphasic system and would do so without exercising any inventive skill. Such a person would also use the same procedure to synthesise the corresponding N-phosphorylated derivatives.

3.2.5 As a result, no inventive step can be recognised with regard to the subject matter of claim 22.

3.3 Claims 1-4 and 25-29

3.3.1 Technical problem

The technical problem that the present invention aims to solve in claims 1-4 and 25-29 is that of providing novel chemical compounds, pharmaceutical compositions containing said compounds and the use of same in the preparation of a drug for treating parasitic diseases.

3.3.2 The proposed solution is to use N-substituted amidines as per formulae (I), (IV) or (V).

3.3.3 Prior art

Document D1: see point 2.2 above.

3.3.4 A person skilled in the art, aware of the disclosure in document D1, namely the antiparasitic activity of non-substituted as well as substituted bis-amidino compounds, would try using amidine derivatives other than those disclosed in document D1 in the preparation of a drug for treating parasitic diseases and would do so without exercising any inventive skill.

3.3.5 As a result, no inventive step can be recognised with regard to the subject matter of claims 1-4 and 25-29.